2-Hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-bezo[α]-quinolizine
[^{11}C]DTBZ

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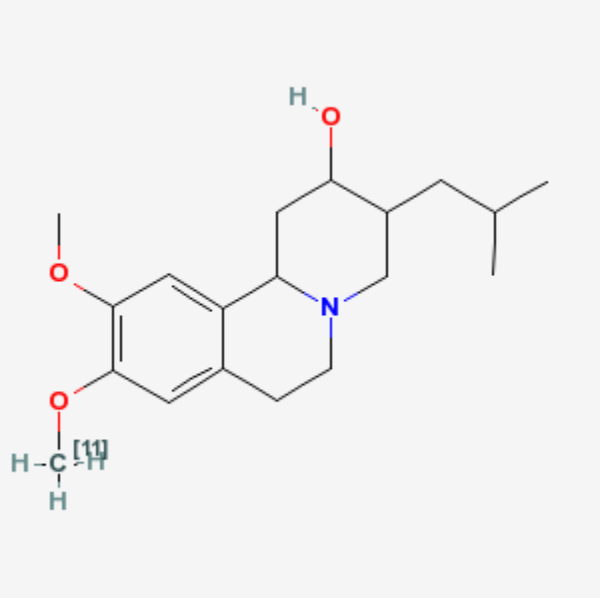
Chemical name: 2-Hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-bezo[α]-quinolizine
Abbreviated name: [^{11}C]DTBZ
Synonym: [^{11}C]Dihydrotetrabenazine
Backbone: Compound
Target: Type 2 vesicular monoamine transporter (VMAT2)
Mechanism: Transporter binding
Method of detection: PET
Source of signal: ^{11}C
Activation: No
***In vitro* studies:** Yes
Rodent studies: Yes
Other non-primate mammal studies: No
Non-human primate studies: No
Human studies: Yes



Click on the above structure for additional information in PubChem [http://pubchem.ncbi.nlm.nih.gov].

Background

[PubMed]

Vesicular monoamine transporter (VMAT2) is present in brain monoaminergic neurons and is responsible for collecting neurotransmitters (dopamine, norepinephrine, and serotonin) from the cytoplasm and storing them in vesicles for synaptic release (1). VMAT2 is therefore an essential regulator of monoaminergic neuronal function. In the brain, VMAT2 is present in high concentrations in the striatum, hypothalamus, substantia nigra, and hippocampus, with low concentrations in the cerebellum and occipital cortex (2). In the striatum, >95% of VMAT2 is associated with dopaminergic neurons (3). Decreases in the VMAT2 level are implicated in movement disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD).

VMAT2 has been studied *in vivo* by positron emission tomography (PET) using [^{11}C]dihydrotetrabenazine (2-hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-bezo[α]-quinolizine; [^{11}C]DTBZ) with selective VMAT2 binding activity in neurons. Binding of DTBZ (VMAT2 inhibitor) to the vesicular monoamine transporter is stereospecific (4). DTZB inhibits monoamine uptake without being transported into the vesicles. The (+)-isomer showed high-affinity *in vitro* binding (K_i = 0.97 ± 0.48 nM) for VMAT2 in rat brain striatum, whereas the (–)-isomer was inactive (K_i = 2.2 ± 0.3 μM). [^{11}C]DTBZ has been developed as a PET agent for the non-invasive study of VMAT2 in the human brain.

Synthesis

[PubMed]

In the report by Jewett et al. (5), [^{11}C]DTBZ was synthesized by alkylation of the 9-hydroxy precursor 2-hydroxy-3-isobutyl-9-hydroxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-bezo[α]-quinolizine) with [^{11}C]methyl iodide. Purification by column chromatography provided a radiochemical yield of 12% based on [^{11}C]CO_2, radiochemical purity >95%, and specific activity of 59-74 GBq/μmol (1.6-2.0 Ci/μmol) in 30 min.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Henry and Scherman (2) reported that saturation binding experiments for [^{3}H]DTBZ in synaptic vesicles from murine striatum gave an estimated K_d value of 2.3-2.7 nM, with a B_{max} of 1.35 pmol/mg protein. *In vitro* binding studies of human postmortem brain with [^{3}H]DTBZ showed high binding in the caudate (766 fmol/mg protein), nucleus accumbens (751 fmol/mg protein), putamen (742 fmol/mg protein), substantia nigra (465 fmol/mg protein), hypothalamus (245 fmol/mg protein), pallidum (115-128 fmol/mg protein), hippocampus (83 fmol/mg protein), and frontal cortex (57 fmol/mg protein).

Animal Studies

Rodents

[PubMed]

Kilbourn et al. (4) reported on regional distribution studies in the brains of normal mice, which showed accumulation of radioactivity in the striatum, hypothalamus, hippocampus, and cerebellum at 15 min after injection of (+)-[^{11}C]DTBZ, [^{11}C]DTBZ, or (–)-[^{11}C]DTBZ. The highest brain accumulation and regional contrast were for the (+)-isomer, with low and uniform uptake for the (–)-isomer. The racemic mixture showed intermediate accumulation. Pretreatment with 10 mg/kg (+)-DTBZ 10 min before (+)-[^{11}C]DTBZ injection in mice significantly reduced accumulation in the striatum and hypothalamus.

Frey et al. (6) performed metabolic studies in rats after injection of [^{3}H]DTBZ. The fraction of unchanged [^{3}H]DTBZ in the blood, liver, and brain, as determined by thin-layer chromatography, was 86, 93, and >99%, respectively, at 15 min after injection.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

Koeppe et al. (7-9) performed human PET studies using Logan graphical analysis, nonlinear least-squares analysis, equilibrium analysis, and a two-tissue compartment model to satisfactorily account for the cerebral kinetics of (+)-[^{11}C]DTBZ. They indicated that the distribution volume (DV), binding potential (BP), and transport constant (K_1) can be estimated from the accumulation of radioactivity in various brain regions as measurements of the integrity of the presynaptic neurons. Chan et al. (10) showed that [^{11}C]DTBZ PET studies in 10 normal volunteers were reproducible by Logan analysis and that the occipital cortex or cerebellum can be used as the reference region. The fraction of unchanged [^{11}C]DTBZ in plasma was 80, 64, and 47% at 10, 30, and 60 min, respectively.

Frey et al. (6) compared [^{11}C]DTBZ PET scans of 15 normal subjects (age range, 22-70 years) with 7 PD patients (age range, 57-79 years; receiving antiparkinsonian medication). Putamen DV decreased with increasing age, corresponding to losses of 0.77% per year in VMAT2 binding. PD patients had significant reductions in DV in the putamen (–61%) and in the caudate nucleus (–43%). Later studies revealed significant correlations of [^{11}C]DTBZ binding reduction with PD severity in motor functions (11). Reduction of striatal VMAT2 binding was shown in patients with multiple system atrophy but not in patients with essential tremor. Bohnen et al. (12) reported significant reductions of DV in the caudate (–33%), anterior putamen (–56%), and posterior putamen (–75%) in HD patients (n = 19) compared with normal controls (n = 64).

Gilman et al. (13) used PET with (+)-[^{11}C]DTBZ to examine striatal VMAT2 density in 20 dementia patients with Lewy bodies (DLB), 25 patients with AD, and 19 normal elderly controls. Six DLB patients developed Parkinsonism at least 1 year before dementia (DLB/PD), and 14 developed dementia before Parkinsonism or at about the same time (DLB/AD). Striatal BP was decreased by 62-77% in the DLB/PD group and 45-67% in the DLB/AD group compared with the AD and control groups. BP was lower in the DLB/PD group than in the DLB/AD group. No differences were found between the AD and control groups. Both DLB groups had an anterior to posterior binding deficit gradient relative to controls (posterior putamen > anterior putamen > caudate nucleus). The DLB/

AD group showed significant binding asymmetry only in the posterior putamen. Therefore, PET with (+)-[^{11}C]DTBZ differentiates DLB from AD, and decreased binding in AD may indicate subclinical DLB pathology in addition to AD pathology.

Internal dosimetry data for [^{11}C]DTBZ in humans are not available in the literature.

References

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